
Human iPSC-Derived Natural Killer Cells Engineered with Chimeric Antigen Receptors Enhance Anti-tumor Activity.

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Public Summary:

Chimeric antigen receptors (CARs) are special receptors that are designed to bind to certain proteins on cancer cells. Genetic engineering of immune cells called T cells, allows the T cells to recognize and kill tumor cells that have the specific protein on their cell surface. CAR-T therapies have revolutionized oncology treatment and FDA has now approved two such therapies for treatment of acute lymphocytic leukemia (ALL) and certain lymphomas. Despite their promising clinical benefits, CAR-T therapies have several shortcomings. Isolation and genetic modification of T cells for current CAR-T therapies are done on a patient-specific basis, which is time-consuming and expensive. These therapies can also sometimes cause severe toxicities in patients. Additionally, treatment of solid tumors with CAR-T cells has been less successful than targeting CD19-expressing tumors. In this research article we show for the first time that human induced pluripotent stem cells (iPSCs) can be engineered at the stem cell-level to produce iPSC-derived natural killer (NK) cells that express CARs. In a mouse model of ovarian cancer, the CAR-NK cells inhibited tumor growth and prolonged survival of mice. Additionally, CAR-NK cells demonstrate in vivo activity similar to that of CAR-T cells, but with less toxicity. Thus, this approach paves the way for a standardized, off-the-shelf, targeted immunotherapy against both relapsed/refractory solid tumors and hematological malignancies.

Scientific Abstract:

Chimeric antigen receptors (CARs) significantly enhance the anti-tumor activity of immune effector cells. Although most studies have evaluated CAR expression in T cells, here we evaluate different CAR constructs that improve natural killer (NK) cell-mediated killing. We identified a CAR containing the transmembrane domain of NKG2D, the 2B4 co-stimulatory domain, and the CD3zeta signaling domain to mediate strong antigen-specific NK cell signaling. NK cells derived from human iPSCs that express this CAR (NK-CAR-iPSC-NK cells) have a typical NK cell phenotype and demonstrate improved anti-tumor activity compared with T-CAR-expressing iPSC-derived NK cells (T-CAR-iPSC-NK cells) and non-CAR-expressing cells. In an ovarian cancer xenograft model, NK-CAR-iPSC-NK cells significantly inhibited tumor growth and prolonged survival compared with PB-NK cells, iPSC-NK cells, or T-CAR-iPSC-NK cells. Additionally, NK-CAR-iPSC-NK cells demonstrate in vivo activity similar to that of T-CAR-expressing T cells, although with less toxicity. These NK-CAR-iPSC-NK cells now provide standardized, targeted "off-the-shelf" lymphocytes for anti-cancer immunotherapy.

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